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THE HISTOLOGICAL DIAGNOSIS OF DERMATITIS HERPETIFORMIS, BULLOUS PEMPHIGOID AND ERYTHEMA MULTIFORME.

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By stressing the importance of acantholysis in the histology of true pemphigus, Civatte (1943, 1949) and the Belgian authors (Dupont and Piérard, 1938, 1949 ; Lapière *et al.*, 1946) made considerable progress in the diagnosis of bullous dermatoses. While their views have been accepted by the majority of skin pathologists, the structural classification of blisters in which acantholysis usually plays no part, such as those of dermatitis herpetiformis (Duhring) and erythema multiforme, remains confused and there are two main causes for this :

(i) The subepidermal position of the blisters which gives all such lesions a uniform appearance.

(ii) Modifications in the clinical concept of dermatitis herpetiformis, recently introduced by Lever and by Prakken, have displaced the notion of a single disease by making a distinction between dermatitis herpetiformis and bullous pemphigoid (Lever) or parapemphigus (Prakken).

To avoid confusion, this distinction can be summarized as follows. Dermatitis herpetiformis is a benign but chronic and recurrent disease whose lesions are pleomorphic and symmetrical. They consist of red blotches and plaques, often urticarial and with circinate margins, on which papules, vesicles and small tense blisters develop either diffusely or in groups. The lesions occur mainly on the extensor surfaces of the limbs, the shoulders, sacral region and buttocks. They

itch and their appearance is preceded by a sensation of tightness or burning. Bullous pemphigoid* is a more uniform disease characterized by larger tense blisters, sometimes haemorrhagic, arising either from normal skin or now and then from a reddened and occasionally urticarial base. Following rupture of the blister, the denuded surface heals readily. Itching is usually absent or slight but the disease has a severe prognosis in elderly or debilitated patients.

Although this distinction is generally accepted from the clinical point of view, there is doubt about the histology. In this paper an attempt will be made to define the differential features of dermatitis herpetiformis and bullous pemphigoid and also of erythema multiforme. The conclusions are based on the study of 9 cases of dermatitis herpetiformis, 20 of bullous pemphigoid and 6 of erythema multiforme. Attempts at microscopic diagnosis between these conditions have failed up till now largely because study has been confined exclusively to the blisters themselves. There has been neglect of the valuable information provided by changes occurring adjacent to them which indicate the manner in which the blisters are formed. It has been shown in two previous papers (Piérard, Dupont and Fontaine, 1957, 1958) how the changes surrounding the blister of dermatitis herpetiformis are so characteristic as to be diagnostic and readily distinguish it from erythema multiforme. In what follows these findings will be restated and a distinction made between these diseases and bullous pemphigoid.

Dermatitis Herpetiformis.

It is well known that the blister of dermatitis herpetiformis is said to be a " tension blister ", generally subepidermal and of small size. It is filled with fluid containing fibrin threads, polymorphs and eosinophils but very few mononuclear or detached epithelial cells. The floor, which to some extent retains its papillary outline, is swollen with oedema and contains numerous cells, fibroblasts, histiocytes, polymorphs, eosinophils, pyknotic nuclei and cellular debris. All this is nonspecific and the more important changes affect the roof whose epidermis is thinned. This thinning, which is often extreme, results from cellular changes which have nothing to do with acantholysis and will be dealt with more fully later.

Much more interesting and specific than the blister itself are the changes in the reddened oedematous zone surrounding it (Fig. 1) The initial lesion, which can be seen at some distance from the blister, consists of a small collection of polymorphs and eosinophils which invade a papilla and accumulate at its summit, separating dermis from epidermis (Fig. 2). Sometimes this infiltrate consists only of bare pyknotic nuclei and cellular debris (Fig. 3). Nearer to

* This name has been retained because it is in general use but it is not above criticism.

the blister, the papillae are swollen by oedema, the dermo-epidermal connections are broken and small cavities are formed containing fluid with polymorphs and a few eosinophils in it. The lower border of the epidermis over each papilla is cleanly detached and the papillary dermis with its capillary is compressed towards the base of the papilla leaving an intrapapillary micro-abscess.

FIG. 1.

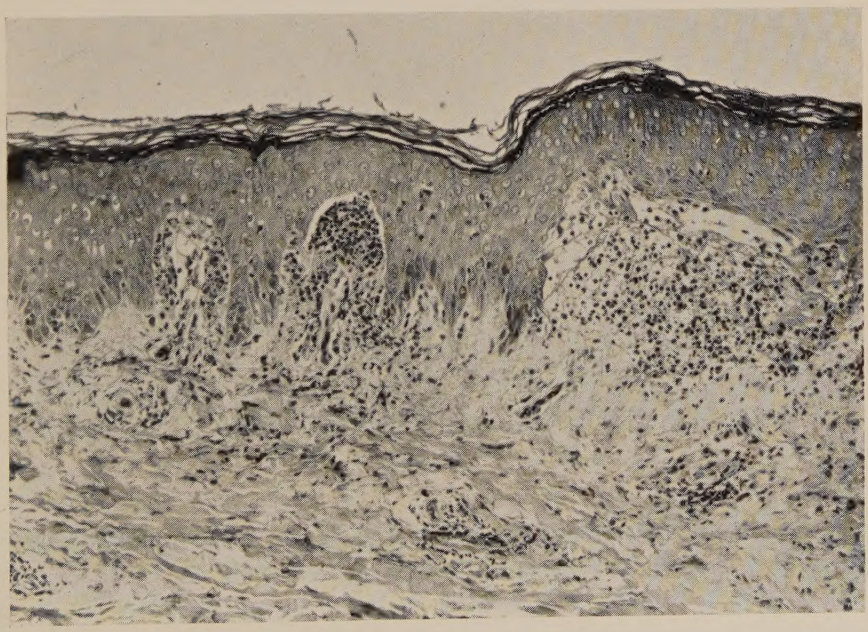

FIG. 2.

The interpapillary ridges of the epidermis remain attached to the dermis at their tips (Fig. 4).

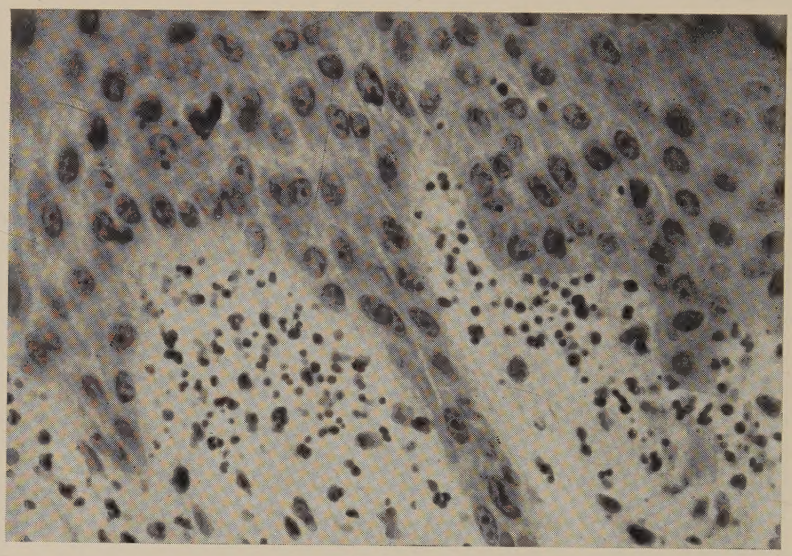

FIG. 3.

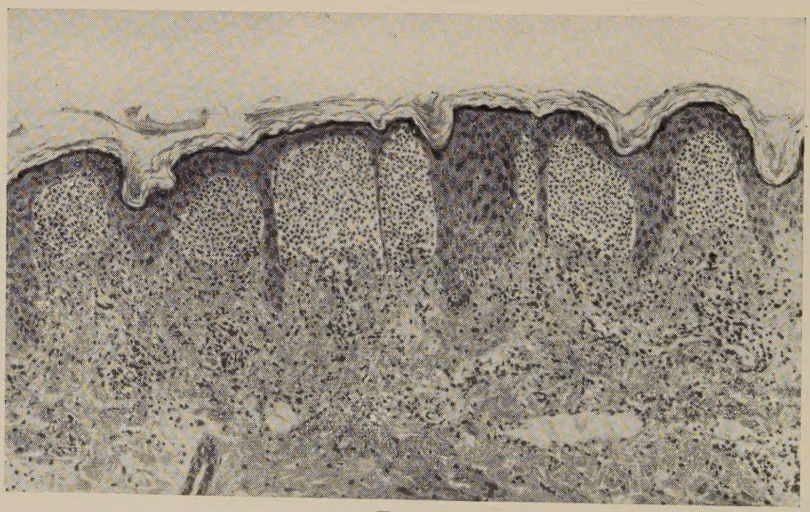

FIG. 4.

Examination of the roof of the blister and of adjacent papillae shows the reason for the epidermal thinning referred to above. It is not just the result of stretching but also of destruction by progressive necrosis of the lower layers of the epidermis which are in contact with fluid containing leukocytes. Some-

times this fluid insinuates itself between the epithelial cells (Fig. 5), separating them from their neighbours and the cells thus isolated become spherical and

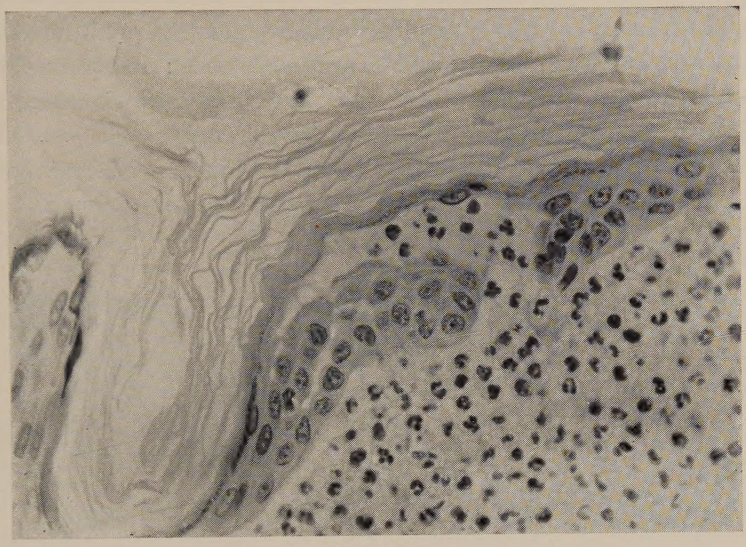

FIG. 5.

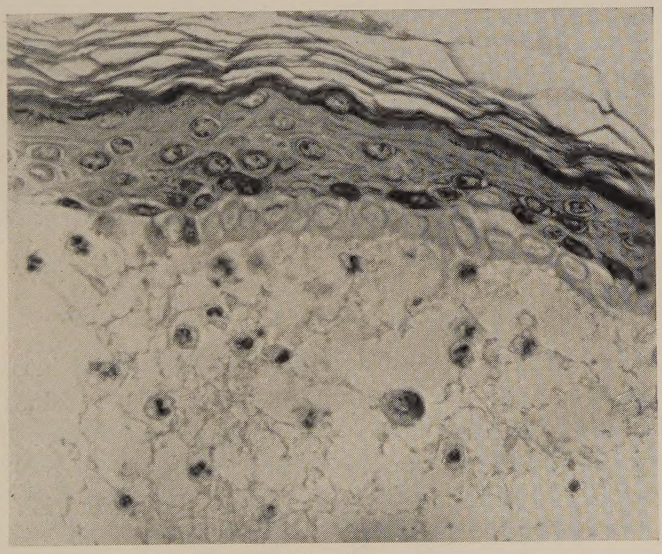

FIG. 6.

float in the fluid. Generally, however, the marginal cells appear to succumb directly to some toxic, perhaps enzymic, action. Their outlines become blurred, their cytoplasm discolours, their nuclei fade and they are reduced to " shadow cells " which fall into the cavity (Fig. 6) and completely dissolve. This explains

both the thinning of the roof and the scarcity of epithelial cells in the blister fluid. This necrosis may also occur in the midst of the epidermis in places where there appears to be no direct contact with blister contents or distended papillae and it then gives rise to hyaline bodies or small vesicles filled with fluid and cellular debris. It is not confined to epithelial cells : in the papillae where the lesions begin, the connective tissue also undergoes necrosis when in contact with leukocyte-containing fluid (Fig. 7).

From these observations, the formation of the blister of dermatitis herpetiformis is explained as follows. A series of micro-abscesses arises at the tips of

Fig. 7.

adjacent papillae. They become distended by oedema fluid into unipapillary microbullae. The epidermis is lifted up, its interpapillary ridges are thinned by necrosis and stretching and finally they dissolve or rupture. The blister is at first multilocular and it is only after several partitions have given way that the cavity enlarges and becomes clinically visible. The formation of the blister is not solely due to tension, but is partly the result of necrosis which occurs where it is in contact with leukocyte-containing fluid. This polymorphonuclear infiltrate plays an important part in the genesis of the bulla. Its role was well demonstrated in two instances in which red papular lesions showed no trace of bullae to the naked eye. Microscopically, however, the presence of the same oedematous papillae filled with polymorphonuclear leukocytes could be detected, just as we have previously described in the neighbourhood of bullae.

Bullous Pemphigoid.

The histology of bullous pemphigoid is very different and here again, both the blister and its surroundings have been studied. The most striking feature is that this is truly a " tension blister ", the epidermis being lifted up by a flow of oedema fluid which detaches it from the dermis *en bloc* (Fig. 8). Changes in epidermal thickness are usually less than in dermatitis herpetiformis and when there is thinning it appears to result chiefly from stretching and flattening of

Fig. 8.

the cells. This is seen particularly clearly in the side walls of the blister where the cells are often heaped up in parallel columns, their nuclei fusiform and hyperchromatic (Fig. 9).

As has been shown by van der Meiren (1953) and Achten (1956), various changes may occur in this detached epidermis and modify its appearance. All intermediary stages may be seen between apparently intact cells and necrotic ones—defective staining, vacuolization, hyalinization of cytoplasm, ballooning and vesicular degeneration. Nuclei may be bell-shaped or crescentic in cells undergoing vesicular degeneration, they may be pyknotic or they may disappear completely. When these necrotic changes affect only small numbers of cells, intraepidermal vesicles are formed. In other cases, the necrosis is limited to the lower border of the detached epidermis but when the whole or a large part of the blister roof becomes necrotic, the appearance is very like that of erythema

multiforme (Fig. 10). When the necrotic changes are unequally distributed and affect only certain regions of the roof they cause an irregular appearance of the epidermis with areas of poor staining and cavitation (Fig. 11).

The contents of the blister are remarkably uniform, consisting of a fibrin network enclosing coagulated serum and a variable number of cells. These accumulate in the lower part of the cavity and consist mainly of eosinophils

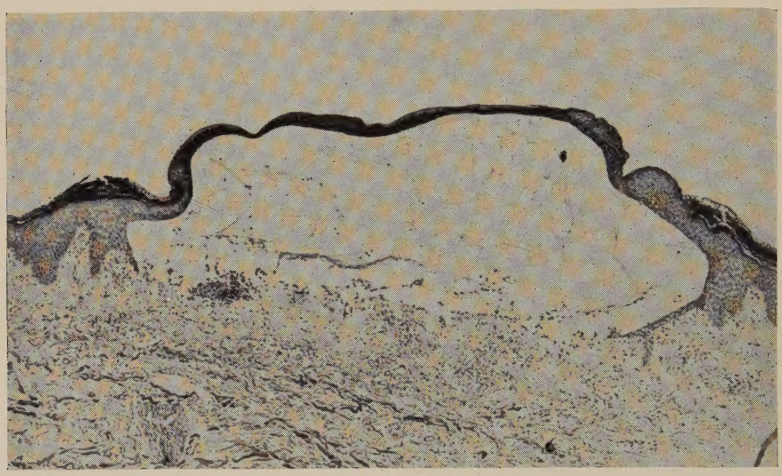

FIG. 9.

FIG. 10.

with a few polymorphs and occasional red cells. Mononuclear leukocytes and free epithelial cells are seldom present. The floor of the blister has a sinuous outline corresponding to the papillary projections and sometimes fragments of epidermis remain attached to it. The whole of the superficial dermis is the site of diffuse oedema which often forms a clear sheath round the vessels. These are distended and surrounded, sometimes densely, by cuffs of lymphocytes and eosinophils. An infiltrate of the same cell types extends diffusely between the vessels, variable in quantity but usually fairly intense.

Fig. 11.

The initial stage of the lesion is seen only occasionally and two forms have been observed. Sometimes it is a simple cleavage produced by a flow of oedema which separates dermis from epidermis, the cavity containing a little amorphous debris but no cells (Fig. 12). On the other hand, the dermo-epidermal cleavage sometimes gives rise to small bullae which are invaded by eosinophils from the beginning (Fig. 13). Contrary to what occurs in dermatitis herpetiformis, the surroundings of the blister offer hardly any diagnostic evidence in bullous pemphigoid. Except for an occasional mild degree of acanthosis, there are often no adjacent changes at all and when there are, they consist only of a direct extension of those beneath the blister. There may be just a few discrete perivascular cuffs or the papillae may be a little oedematous and infiltrated by eosinophils, the overlying epidermis showing spongiosis and leukocytic invasion (Fig. 14). However extensive the infiltration may be, it never collects at the tips of the papillae to form microabscesses like those of dermatitis herpetiformis.

There are thus definite differences between dermatitis herpetiformis and bullous pemphigoid but it is the surroundings of the blister which show them more than the structure of the blister itself. In fact, the only distinguishing

FIG. 12.

FIG. 13.

feature in the blisters is the necrotic erosion of the epidermis seen in dermatitis herpetiformis and this may be hard to detect. There is however no difficulty with the peribullous changes. If the papillae are swollen and cleanly detached and have at their tips micro-abscesses of polymorphs and eosinophils which do

not penetrate the epidermis but compress the dermal papilla and its capillary towards the base, that is dermatitis herpetiformis. If on the other hand the papillae are devoid of lesions, or if there are a few oedematous papillae diffusely infiltrated by eosinophils which invade and disorganize the lower layers of spongiotic epidermis, that is bullous pemphigoid.

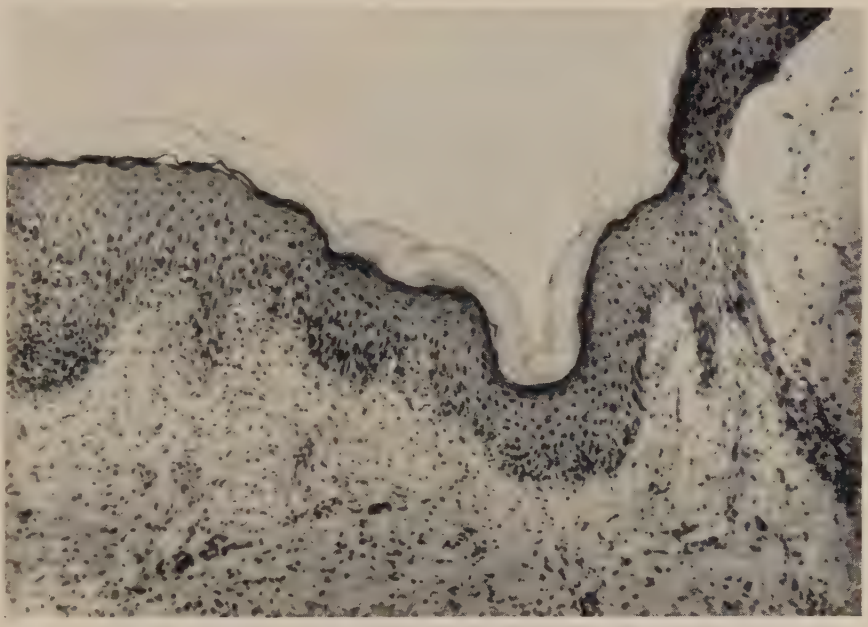

Fig. 14.

Bullous Erythema Multiforme.

The distinction between dermatitis herpetiformis and erythema multiforme is relatively easy, but the features which distinguish erythema multiforme from bullous pemphigoid are slight. In erythema multiforme, some lesions have a pathognomonic appearance as Civatte has shown, the roof of the blister being entirely necrotic (Fig. 15). However, this feature is not always present and furthermore, certain lesions of bullous pemphigoid show something very like it (Fig. 10).

In all the erythema multiforme blisters studied, the cavity has been subepidermal. The floor, which sometimes has shreds of epidermis attached to it, retains its papillary outline and these papillae, as well as the dermis beneath them, contain a predominantly lympho-histiocytic infiltrate, with possibly a few polymorphs or eosinophils. The blister fluid contains similar cells, with perhaps rather more polymorphs. The roof of the blister usually shows severe changes, its lower border having an irregular margin due to necrosis of groups

of cells. The same process can be seen occurring in the middle of the remaining epidermis and producing small cavities.

The comparison of the actual blisters of these various conditions is often inconclusive and to find distinctive features of erythema multiforme, the

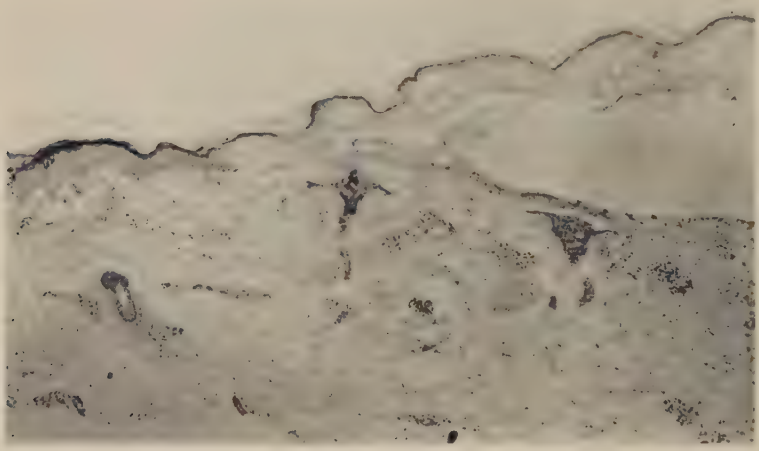

Fig. 15.

Fig. 16.

surroundings of the blister must be studied. These peribullous changes extend over several papillae on either side and affect both the epidermis and the papillary dermis (Fig. 16). The main feature of the epidermis is the frequency of spongiosis and the presence of a transepidermal exudate, sometimes very

intense. The spongiosis is variable, sometimes so intense as to cause eczematoid vesicles, sometimes confined to small isolated foci, and sometimes it is absent altogether. The transepidermal infiltration seems always to be present and is composed mainly of lymphocytes with a few polymorphs. It upsets the basal layer and renders it indistinct, invades the lower layers of the epidermis and often causes hyaline necrosis of cells. If a group of cells is affected in this way, a vesicle is formed by necrosis rather than by accumulation of fluid. The microscopic appearance of the dermal papillae is also influenced by the oedema and infiltrate, their contours being ill-defined as a result of the spongiosis and in-

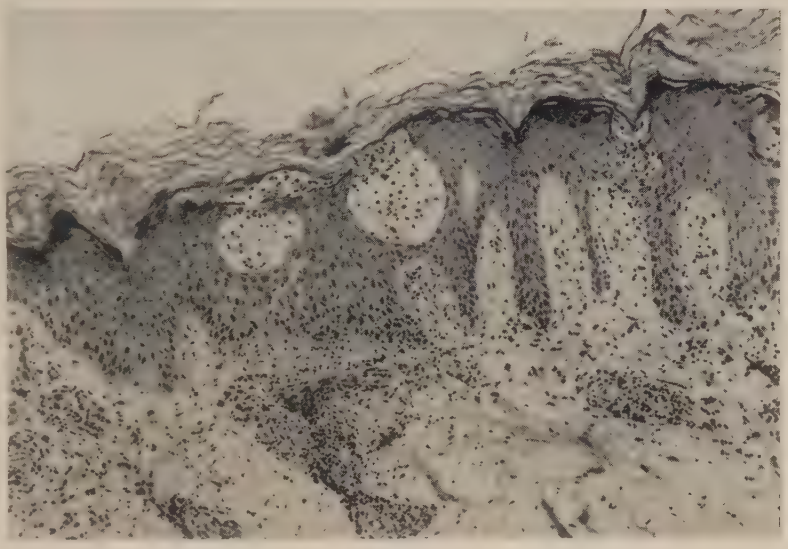

Fig. 17.

filtration of the overlying epidermis. The papillary oedema is often intense, the full depth of the papilla is infiltrated diffusely and its capillary and connective tissue are not compressed towards the base. The cells of the infiltrate are predominantly mononuclear but there may be a few polymorphs among them (Figs. 17 and 18).

The histological appearance is clearly very different from that of dermatitis herpetiformis in which the papillae are sharply outlined, epidermal infiltration and spongiosis play little or no part and the polymorph infiltrate forms microabscesses at the tips of the papillae, detaching the epithelium and compressing the connective tissues towards the base. The features which distinguish erythema multiforme from bullous pemphigoid are less obvious. Papillary infiltration, spongiosis and infiltration of the epidermis are seen in both conditions and the differential diagnosis is based mainly on the distribution and composition of the infiltrate. While in erythema multiforme the peribullous changes

extend over several papillae and the inflammatory cells are mostly mononuclear, in bullous pemphigoid the peribullous changes are generally less widespread and characteristically there is always a considerable proportion of eosinophils, both in the infiltrate and in the blister fluid.

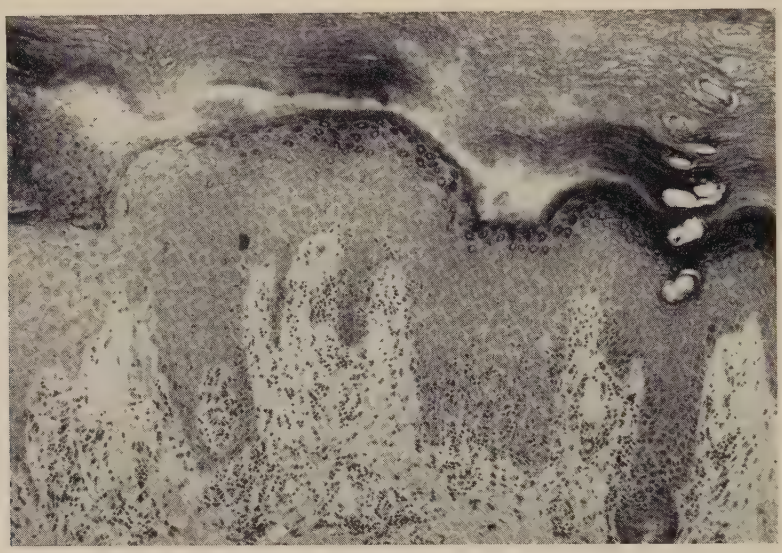

Fig. 18.

Conclusions.

Dermatitis herpetiformis (Duhring) has a specific histology, quite different from that of bullous pemphigoid and bullous erythema multiforme.

The histology of bullous pemphigoid has much in common with that of erythema multiforme—the same tendency to necrosis of the blister roof and in some cases similar papillary oedema and infiltration, spongiosis and transepidermal infiltration. The distinction between the two is made chiefly on the limited extent of the peribullous changes and the almost exclusively eosinophil infiltrate of bullous pemphigoid.

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IS EOSINOPHILIA OF DIAGNOSTIC IMPORTANCE IN DERMATITIS HERPETIFORMIS?

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Funk (1895) first drew attention to the increase of eosinophil cells in the blood and skin of patients with dermatitis herpetiformis. Leredde and Perrin (1895) described the presence of large numbers of eosinophils in the upper corium and vesicles. Hallopeau and Lafitte (1896) emphasized the diagnostic value of the simultaneous appearance of an increase in eosinophil cells in the circulating blood and bleb serum in cases of dermatitis herpetiformis. Since these reports a great deal of attention has been paid to the presence of eosinophil cells in this disease. Authoritative dermatologists were reserved and sometimes contradictory in their attitudes. MacLeod (1915) said it was by no means invariable even at the height of the disease but in his textbook (1920) he laid considerable emphasis on its importance. Whitfield (1915) and Graham Little (1915) also attached no importance to the phenomenon but the former in his textbook (1921) stated that " one almost invariably finds a pronounced eosinophilia of the circulating blood ". Other authors (Fordyce, 1897 ; Jamieson, 1898 ; Pringle, 1898 ; Galloway, 1898 ; Ravogli, 1900 ; Knowles, 1907 ; Sequeira, 1919 ; MacKenna, 1923 ; Roxburgh, 1941 ; Gray, 1941 ; Becker and Obermayer, 1943 and Cranston Low and Peterkin, 1949) considered the eosinophil count unimportant in diagnosis. Ormsby and Montgomery (1943) said it was just as marked in various types of atopic eczema and other dermatoses as in dermatitis herpetiformis, whilst Goodman (1941) stated that although characteristic it was not pathognomonic. Eyster and Kierland (1951) reported the results of eosinophil counts in 116 patients (mostly single readings). The count was over 4% in 46 (39·7%) and over 10% in only 14 (12%). The count showed no relation to duration and had no prognostic value. In general the severity of the case was reflected by the degree of eosinophilia. Where more than one count was made the eosinophilia tended to be more pronounced when the disease was active. Russell and Thorne (1957) in a well documented series indicated that pronounced eosinophilia occurred in herpes gestationis, varying with the state of activity of the disease. However, they considered that the latter differed from dermatitis herpetiformis, an opinion with which I agree. In view of these confusing statements it seemed that a critical examination of this phenomenon in dermatitis herpetiformis was merited.

Investigation.

Two methods of counting eosinophils were used.

(i) *Film and percentage method.*—A total leucocyte count was made in the usual way. A Leishman stained blood film was examined and a differential leucocyte count made of 200–500 cells, the number of eosinophil cells being expressed as a percentage of the leucocytes and the total eosinophil count calculated from the total leucocyte count. Most of the films were made on glass slides but latterly coverslip preparations were used. All the counts were made by the same observer with the exception of the " sulphonamide " control group where the counts were made by an R.A.M.C. laboratory technician.

(ii) *Absolute eosinophil count.*—A conventional white-cell pipette and a Fuchs-Rosenthal or Neubauer counting chamber were used. Blood was drawn into the pipette to the 0·5 mark and the diluting fluid to the 11 mark. The diluting fluid used was Manner's stain which was found to be very satisfactory. It tended to deteriorate if kept too long and a fresh supply was used every month. The pipettes were shaken by hand for two minutes. At first four separate counts were made from the same pipette, the counting chamber being cleaned and recharged each time. Latterly, however, it was found that two such counts gave satisfactory figures. All the counts were made by the same observer.

Subjects (i) *Controls.*

(a) *Normal persons.*—Ninety-seven counts were done on normal persons the majority of whom were between the ages of 19 and 30.

(b) *Others.*—Twenty cases of other skin diseases chosen at random. Fifteen cases of sulphonamide dermatitis were also seen during the war and detailed counts of them were also made.

(ii) *Dermatitis herpetiformis.*—Fifty-one cases of this disease were investigated under various conditions and using the two methods outlined above.

Before giving the results it is necessary to consider shortly what are the normal figures for each method. According to Whitby and Britton (1957) the normal figures for the film and percentage method are 1–4% of the total leucocyte count with an upper limit of 400 eosinophil cells per cu.mm. This definition of the normal count is generally accepted though Dacie (1958) gave the limits as 40 to 440 per cu.mm. This latter figure has been taken as the normal in the present series of counts using this method. Using the absolute count, Discombe (1946) found the normal range to be 0–240 cells per cu.mm. He stated that if more than 325 cells per cu.mm. were found, eosinophilia was present. Rud (1947) using a similar technique made 13,000 counts on 123 normal persons and found the average normal figure for males to be 161 and for females 166 per cu.mm. Rud gave as the maximum normal figures 300 for men and 325 for women, which correspond very closely with the findings of Discombe. Fisher and Fisher (1951) obtained essentially similar results. It can be taken that the normal maximum figure of 325 eosinophils per cu.mm. obtains for normal persons by this second method.

Results.

These are given in Tables I and II. Those of counts made in normal persons in Table I revealed a higher than normal level in five persons, the actual figures ranging from 485 to 824 eosinophil cells per cu.mm. In the corresponding group in Table II four other persons had slightly raised eosinophil counts (361–444 per cu.mm.). In the two groups there were only three individuals common to

TABLE I.—*Results of Eosinophil Counts Using the Film and Percentage Method.*

Group examined.	Number of persons.	Number of counts.	Eosinophils	
			Mean percentage.	Calculated mean total.
Normal	33	41	2·94	247
Dermatitis herpetiformis	33	298	3·6	267
Sulphonamide dermatitis	15	67	4·17	403
Other skin disorders	20	56	3·86	267

TABLE II.—*Results of Eosinophil Counts Using the Absolute Method.*

Group examined.	Number of persons.	Number of counts	Mean value of total eosinophils.
Normal	56	56	133
Dermatitis herpetiformis	46	192	170

both groups and none of them showed an increase. As the counts were taken from a random sample these slightly elevated readings have not been excluded from either group. Statistical comparison of the various groups in Table I showed in the first place that there was no significant difference between the mean eosinophil counts in dermatitis herpetiformis and normal persons ($t = 0{\cdot}351$; $P = 0{\cdot}8$). Similarly there was no significant difference between the mean counts in dermatitis herpetiformis and that of a random sample of other skin diseases including eczema ($t = 0{\cdot}017$; $P = 0{\cdot}8$). On the other hand the mean eosinophil count in sulphonamide dermatitis was significantly higher than that of dermatitis herpetiformis ($t = 2{\cdot}767$; $P = 0{\cdot}01$). In Table II analysis showed that in the two groups also there was no significant difference in the eosinophil counts ($t = 1{\cdot}57$; $P = 0{\cdot}20$).

DISCUSSION.

The statements made above require amplification to appreciate their significance fully. The first factor to be considered is the method of counting eosinophils. There is no doubt that the absolute count using a special diluting fluid gives a more precise estimation than the film and percentage method. It is easier and quicker to carry out and there are fewer opportunities for technical error. Using the film and percentage method Discombe (1946) asserts that an increase in circulating eosinophils can only be detected with certainty if 1000 or more cells in a film are enumerated on coverslip preparations. This is a tedious procedure and few laboratories examine more than 200 cells and not all use coverslip preparations. In the present series of investigations, usually 200 cells were counted but in some cases, where the distribution of cells on the film seemed uneven, as many as 500 or more were examined. Taking the factor of the actual method used into account there seemed in this series to be

a slightly greater difference between the mean counts in the groups in Table II than that between the same groups in Table I. Neither difference, however, was statistically significant.

An important factor with regard to the film and percentage method is the manner of expressing results. So often one reads such reports as " the eosinophil count was 6%, which indicates a mild eosinophilia ". Does it ? Such a statement is meaningless unless the total leucocyte count is given. Then the actual total of circulating eosinophils can be calculated to ascertain if there really is an increase. Even when both figures are given it is not infrequently stated that eosinophilia is present when in fact it is not. Simple arithematical calculation can demonstrate this. Suppose a hypothetical case was reported as having 7% eosinophils present, with a total leucocyte count of 5,000. A superficial glance at the eosinophil percentage suggests eosinophilia but there would actually be 350 per cu.mm., which is well within the normal range. The reverse can also be true, e.g. a percentage eosinophil count of 4, with a total leucocyte count of 15,000 gives a figure of 600 eosinophils per cu.mm. Whilst it must be remembered that the number of circulating eosinophils is not influenced by the level of the leucocyte count, to ascertain the actual level of the former, figures for the latter are necessary. This is one of the principal reasons why there has been hitherto such confusion and uncertainty about eosinophilia in dermatitis herpetiformis. As a practical demonstration of this, the figures in the present investigation afford ample evidence. One patient, who actually had eosinophilia, had an eosinophil percentage of 4 and without further information might easily have been said not to have eosinophilia. On the other hand no fewer than 39 instances occurred where the percentage count was above normal (4%). The figures were 11% in 2 cases, 10% in 2, 8% in 2 and 7% in 5 of these 39. In actual fact none of these 39 counts showed an elevated level in absolute number of circulating eosinophils. All of them might have been labelled as indicating eosinophilia.

Examination of the actual counts made in this series reveals that taken as a group there is no significant difference between the eosinophil counts in patients with dermatitis herpetiformis and normal persons. However, a scrutiny of the individual results showed that in the series of dermatitis herpetiformis cases three patients had persistently high counts. Ten other patients had one count above normal and two had three abnormally high levels. In none of these twelve cases did the levels of the eosinophil count reflect the state of activity of the disease. It was noted, however, that the three patients with persistently high counts were all rather severe cases and this supports the contention of Eyster and Kierland (1951) that high levels of eosinophilia tend to reflect the severity of a particular case. In contrast, the cases of sulphonamide dermatitis, with an allergic aetiology, showed a mean eosinophil count significantly higher than that in dermatitis herpetiformis. Furthermore the level

of eosinophilia had a distinct relation to the activity of the disease. At the height of the allergic reaction the eosinophil counts were at their highest and when recovery began to be evident the eosinophil count began to fall. In dermatitis herpetiformis, on the other hand, the highest count in a series might easily be found when the disease was only minimally active or even under complete control. In fact the eosinophil count in dermatitis herpetiformis behaves like the count in normal persons with wide fluctuations from day to day and even from hour to hour independent of the degree of activity of the disease.

As a further test of the variation of the eosinophil level, a group of thirteen cases was examined immediately before taking 100 mg. of dapsone (treatment having been withheld for 24 hours previously) and at 15-minute intervals for an hour afterwards. These tests were carried out between 2 p.m. and 4 p.m., which is one of the periods recommended by Rud (1947) in which a daily average count can be obtained. There was no significant trend for the count either to rise or fall. In some cases there was a slight rise followed by a fall, in others the reverse was true and in some the count remained more or less steady. Some of the cases had relapsed when the tests were carried out, others were quiescent but the state of the disease made no obvious difference to the counts. In one severe case the counts remained at a persistently high level, averaging about 1400 per cu.mm.

Summary.

It is concluded from these series of eosinophil counts that with the exception of severe cases, the count is not raised in dermatitis herpetiformis and as a group there is no significant difference from normal. The level of circulating eosinophils is, therefore, of no diagnostic importance in dermatitis herpetiformis. The level of the eosinophil count does not reflect the state of activity of the disease and has no prognostic significance in any individual case. In severe cases, however, the count tends to be persistently raised, often to moderately high levels.

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RECURRENT GENITAL AND ORAL ULCERATION WITH EOSINOPHILIA.

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In a series of publications, Behçet (1937, 1938, 1940) grouped together as an entity the diagnostic triad of recurrent but transient oral ulceration, genital ulcers and relapsing iritis or iridocyclitis, the latter being inconstant. The syndrome now bears his name although Whitwell (1934) had previously described the association of ulceration of the mouth and genitalia with iritis, together with skin lesions akin to erythema nodosum.

More recently, the syndrome, even incomplete, has been accorded the status of a disease (Curth, 1946 ; Phillips and Scott, 1955) and various additional complications have been described. Of these, skin lesions appear most frequently and of 33 cases reviewed by France *et al.* (1951), erythema nodosum was present in 11 and pyoderma in 15. Thrombophlebitis of large or small vessels occurs in twenty-five per cent of cases, muscle and joint pain is common although obvious joint swelling is rare, and the nervous system may be affected (Pallis and Fudge, 1956 ; McMenemey and Lawrence, 1957). These complicating lesions sometimes precede the classical syndrome and may be the main presenting features of the disorder. Fever, lassitude and malaise may also be present during the more acute phases.

Formerly, most of the earlier recorded instances involved patients who had lived in the Levant but the condition, while still rare, is now being reported from many other parts of the world. It apparently most frequently affects adults in the third decade (Berlin, 1944).

The following case is reported because of a comparatively late age of onset and a marked degree of eosinophilia for which no other cause could be demonstrated.

Case Report.

An unmarried man aged 54, had had recurrent conjunctivitis for the past 20 years. During the second world war he served with the Polish Army in the Middle East, where he suffered from frequent intestinal disturbances but had no febrile illness, asthma or rheumatic symptoms.

In the spring of 1955, at the age of 48 he began to have attacks of ulceration of the penis and mouth. These usually persisted for two to three weeks and recurred after intervals of three to five weeks. He thought the attacks followed sexual excitement and various worries connected with his work. He believed that his father, who died in his seventy-eighth year, also suffered from the same ailment and was known to have an " abnormal blood ". There was no other relevant family history. Extensive

treatment with penicillin and sulphonamides had been given, but without effect on the course of the illness.

When he was first seen in April 1957, his current and most severe attack had already lasted two months without remission. He was then afebrile and showed numerous vesicles, erosions and ulcers on the oral mucosa, gums and hard palate. Ulcerative balanoposthitis, oedematous phimosis and bilateral blepharo-conjunctivitis were also present. The nostrils and nasal mucosa were normal and the skin, regional lymph glands, joints and nervous system showed no abnormality. The spleen and liver were not enlarged.*

A blood examination at this time showed normal haemoglobin, red cell and platelet levels, and the following white cell count : total W.B.C. 13,650 per cu. mm., neutrophils 27%, lymphocytes 11%, monocytes 2%, basophils 2% and eosinophils 58%. With only short periods of freedom from symptoms, the genital and oral ulceration persisted for the next twelve months, whilst the white cell count gradually crept up, reaching a maximum after nine months of 33,000 per cu. mm., neutrophils 5%, myelocytes 0·5%, lymphocytes 2·5%, monocytes 1%, basophils 1% and eosinophils 90%.

Systemic treatment with prednisone soon resulted in the appearance of more immature white cells in the peripheral blood and was in consequence withdrawn. While it was continued, the steroid had no clinical effect on the symptoms, but these began to remit a few weeks later with vitamin C therapy, and ulceration ceased completely about one year after observation began. The remission has continued with only minor recurrences. With the decline of symptoms, the degree of eosinophilia abated somewhat, but the general blood picture has changed only slightly and the following recent count is typical of those obtained during the three years of subsequent surveillance : Hb. 13·1 g. per 100 ml., W.B.C. 22,700 per cu. mm., neutrophils 9%, lymphocytes 10%, monocytes 1%, eosinophils 80%. The patient nevertheless reports that he has " never felt so well in his life ".

Laboratory Investigations.

Sternal marrow aspirates were examined before and after the corticosteroid therapy and found to be similar on both occasions with an extreme degree of reactive hyperplasia. Activity was predominantly devoted to eosinophil maturation, yet all stages, whilst grossly exaggerated, appeared to be normal. Erythropoiesis was normal although overshadowed and formation of neutrophil granulocytes was considerably restricted. There was no morphological evidence of functional abnormality and nothing to indicate leukaemia or any allied myeloproliferative dyscrasia.

Investigations of the peripheral blood stream showed a variable red cell pattern, slight reticulocytosis and some degree of anisocytosis with occasional polychromasia, but there has been no evidence of any deficiency syndrome and no anaemia.Throughout the period of study, the eosinophil count has ranged from 70% to 90% in a total circulating white cell count of 15,000 to 33,000 per cu. mm. Direct eosinophil counts paralleled those assessed by the differential method. Latterly, a consistent absolute neutropenia has been noted and, although this is not reflected by any increased susceptibility to infection, it may indicate the insidious development of marrow failure.

Repeated investigations for circulating heterophil and atypical warm or cold acting antibodies were negative. The L.E. phenomenon could not be demonstrated and all standard tests of haemolytic function were within normal limits. The blood W.R. and Kahn reactions were consistently negative ; psittacosis-LGV complement fixation tests were negative and antibody fixation studies (Evans *et al.*, 1957) did not support any viral aetiology. The blood urea was 40 mg. per 100 ml. Tests of liver

* [The case was presented as one of Behçet's syndrome at the meeting of the Section of Dermatology of the Royal Society of Medicine, London, in May, 1957 ; Merenlender, 1957.]

function showed normal thymol turbidity with an alkaline phosphatase level at the upper limit of normal. A total serum protein amounted to 7·6 g. per 100 ml. with 3·3 g. albumin and 4·3 g. globulin. There was a slight increase in α_2- and γ-globulins on electrophoretic analysis. Initially, the Quick single stage " prothrombin " time was normal but recent readings show a consistent delay of 4 secs. when compared with a normal control of 12 secs. The plasma uric acid was slightly raised at 5·6 mg. per 100 ml. Frequent bacteriological examinations of sputum, faeces and urine and particular searches for parasitic infestation were negative. Occult blood was not found in the stools.

Other Investigations.

Throughout three years of observation, numerous X-ray plates of the chest were studied. At no time has there been anything to suggest the changes seen in the various manifestations of Loeffler's syndrome. We are indebted to Dr. Nicholas Hajdu for reviewing all the plates and giving the following comment. " A few calcified lymph nodes are present in the right hilum. There are a number of linear shadows at the junction of the right upper and middle zones which, in the lateral film, are hidden by bony structures, but I think that they are no doubt situated in the apical segment of the lower lobes. In view of the presence of lymph node calcification in the right hilum the most likely explanation of the linear shadows is that they represent clinically insignificant residual fibrosis in the segment which was originally the seat of a primary complex. Radiologically, there is no ground to assume that eosinophilic infiltration plays a part in producing these shadows."

No causative agents of other forms of tropical eosinophilia could be demonstrated. Frequent clinical and laboratory examinations failed to show any of the other stigmata of polyarteritis nodosa. Serum examined for the neutralizing antibody described by Evans *et al.* (1957), gave a negative result and at no time were inclusion bodies seen in smears nor was there any other specific evidence of viral activity. Electrocardiographic tracings were within normal limits. Although lead V_4 showed slight right ventricular preponderance there was nothing to suggest eosinophilic infiltration of the myocardium.

Discussion.

The aetiology of Behçet's disease remains obscure. Behçet (1938) found very small reddish-violet extra- and intra-cellular bodies which he compared with the elementary bodies of smallpox. His belief in a viral origin has been supported more recently when Sezer (1953) first claimed the isolation of a possible causative virus and Evans *et al.* (1957), obtained a virus from the brain of a patient who died from a neurological complication. These latter investigators also showed that the sera of six out of eleven patients with Behçet's disease had detectable neutralizing antibody.

That the syndrome may reflect an allergic response associated with hypersensitivity has also received support in the past (Koch, 1950). Linton and Saint (1956) contrasted the mucocutaneous changes in the Reiter and Stevens-Johnson syndromes with those seen in Behçet's disease and attributed all three to " hypersensitivity ", while Wadia and Williams (1957) in reviewing the neurological complications, singled out the occurrence of erythema nodosum to support the view that there was a dual basis of both viral infection and allergy.

There seems to be little support for the suggestion of hormonal imbalance (Moseley, 1941) and thrombophlebitis, when it occurs, appears to be only a sequela (France, *et al.*, 1951).

In dealing with systematized lesions of doubtful origin, it is difficult to avoid the adoption of some such general term as collagen-vascular disease (Phillips and Scott, 1955), and an eosinophilia would be consistent with the visceral angiitis of a collagen disorder such as polyarteritis, or of gross allergic or hypersensitive states. Eosinophilia, however, is an uncommon finding in Behçet's syndrome. Silfverskiöld (1951), for example, reported a case with persistent eosinophilia reaching 35% of an unspecified total white cell count, while France *et al.* (1951), found the eosinophil and plasma protein levels to be within normal limits in reviewing thirty-three patients.

In the case now described, the unusually high degree of eosinophilia is noteworthy. Leukaemic changes have been expressly excluded, although it is doubtful whether eosinophilic leukaemia exists as an entity other than as a transient manifestation of chronic myeloid leukaemia. Alkaline phosphatase studies on the circulating neutrophilo granulocytes have repeatedly shown a high activity in keeping with a reactive condition. Familial eosinophilia cannot be entirely ruled out here, particularly as the patient's father was said to have had an abnormal blood. Unfortunately, family studies have been impossible, but the intensity and degree of the eosinophilia, apparently fluctuating with the disease, renders unlikely the possibility of a coincidental familial anomaly. Careful investigation has failed to reveal any evidence of the alveolar capillary block syndrome (Eldridge, 1958), in which it is now suggested that all stages of the Loeffler syndrome and polyarteritis nodosa share a common pathophysiological basis of a hyperimmune hypersensitivity reaction similar to that induced in rabbits (Rich and Gregory, 1943). Despite the patient's incarceration as a prisoner of war in Tobruk and his service in North Africa, there has been no evidence of any infestation. At no time has there been any peripheral thrombophlebitic episode and no neurological complications.

The presence of such gross eosinophilia also raises the possibility of the so-called disseminated eosinophilic " collagen disease " (Engfeldt and Zetterström, 1956), described by Zuelzer and Apt (1949) as occurring in young children. Subsequent reports involving adults have appeared in the literature but this fatal condition invariably shows diffuse systematized lesions, often with the changes of Loeffler's syndrome, hepatosplenomegaly and hypergammaglobulinaemia. With the exception of a slight increase in α_2- and γ-globulins, none of these changes has appeared in our patient. Occasionally gross eosinophilic infiltration leads to visceral damage with electrocardiographic changes. It might be inferred in this patient that the prolonged prothrombin activity is an index of eosinophilic liver infiltration but this is not supported by any other test of liver function.

This series of negative findings in a case of recurrent genital and oral ulceration is somewhat daunting. It is, however, of interest that such a gross eosinophilic reaction has been provoked and such a finding would lend support to the view that the syndrome is an exaggerated allergic response occurring in a hypersensitive individual.

With the current emphasis on possible autoimmune mechanisms in the aetiology of obscure disease, it remains only to state that repeated examinations have failed to reveal atypical antibody activity, using standard haematological methods with trypsinized and tanned erythrocytes and by animal inoculation.

The appearance together of genital and oral ulceration as in this patient is not uncommon and it is felt that not all such cases should be regarded as examples of Behçet's syndrome. If this term is to be used it might perhaps best be reserved for those cases where the syndrome occurs complete with a progressive uveitis. If a specific causal organism is confirmed to account for any group of such cases, only then might it be appropriate to call the condition Behçet's disease.

Summary.

A case is described of recurrent genital and oral ulceration initially presenting at the age of forty-eight.

An associated eosinophilia was noted, amounting to 90% of 33,000 per cu. mm. total white cells, while the disease was clinically at its height. This reaction supports the view that the condition may be a manifestation of hypersensitivity. Investigations for viral activity and autoimmune antibodies proved consistently negative.

Requests for reprints should be addressed to Dr. Schwartz.

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TOXIC EPIDERMAL NECROLYSIS IN A PATIENT WITH PULMONARY ASPERGILLOSIS.

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In 1956 Lyell described four patients in whom a toxic eruption closely resembled scalding of the skin. The main pathological feature was necrosis of the epidermis and he introduced the term " toxic epidermal necrolysis " for the condition. Similar cases have been reported by Lang and Walker (1956, 1957), Rook (1957), Gill (1958), Catto (1959), Evans (1959), Frain-Bell and Koblenzer (1959), Walker (1959), Potter (1960) and Browne and Ridge (1961). It is likely that the eruptions described by Ruskin (1948) with methylphenylethyl hydantoin, by Jaeger (1951) with gold salts, by Degos *et al.* (1953) with subacute monocytic leukaemia, by Jaeger and Delacretaz (1955) with Hodgkin's disease, by Kennedy *et al.* (1957) with antipyrin and by Ellis (1957) with acetazolamide, were of the same type. We report a further case in which pulmonary aspergillosis was found at autopsy.

Case Report.

A man aged 85 fell at home and fractured the right femur. He was admitted to hospital where radiography confirmed the fracture and showed the presence of Paget's disease of the pelvis and femur. The latter was pinned two days after and he was transfused with one pint of blood because the haemoglobin was 66%.

Eleven days after his fall he developed bilateral conjunctivitis and peeling of the skin of the trunk. The temperature was 98° F. The same evening the temperature rose to 102° F. and examination of the chest revealed a right-sided basal pneumonia. The following day the peeling was more marked and resembled that of extensive scalding of the skin. The patient died two days after the onset of the eruption. The blood urea was 66 mg. per 100 ml. on admission and 118 mg. per 100 ml. on the day before death. He received an injection of anti-tetanic serum on admission, and injections of atropine and pethidine on the day of operation. An injection of paraldehyde was given two days before the onset of the rash. When the conjunctivitis and peeling had started, he was treated with sulphacetamide eye drops and injections of penicillin.

Autopsy.

External appearances.—The body was that of a spare, elderly man with a recent surgical scar over the right upper thigh. Extensive exfoliation of the epidermis had occurred over approximately 50% of the body surface. The raw areas appeared erythematous and a few patches had the " tanned " coagulated consistency of burned skin. There was a strong resemblance to scalds. Bilateral cataracts and bilateral inguinal herniae were present.

Respiratory system.—Separable fibrous adhesions obliterated both pleural sacs. Both lower lobes showed nodular bronchopneumonic consolidation. The trachea and

bronchi contained viscid muco-pus and showed chronic inflammatory changes. The mediastinal lymph nodes were normal.

Cardiovascular system.—The pericardium was normal. The heart weighed 400 g. and showed a slight degree of left ventricular hypertrophy. The coronary arteries displayed patchy, constrictive, calcified atheroma. Slicing the myocardium revealed minute foci of ischaemic fibrosis. The pulmonary artery was normal. The aorta showed patchy calcified atheroma.

Central nervous system.—The scalp and meninges were normal. The basal vessels showed slight patchy atheroma. Slicing the brain revealed a narrow band of old cystic softening in each putamen.

Skeletal system.—The right femur showed a comminuted pertrochanteric fracture which had been nailed and plated. A large haematoma was associated with the wound. The skull showed osteoporosis and increased vascularity due to Paget's disease of bone. The spine and both femora also showed osteoporosis.

Alimentary, urogenital and endocrine systems.—These were normal apart from slight nephrosclerosis and lipoid depletion in the adrenal cortices.

Histology.

Skin.—The more severely affected areas showed total necrosis of the epidermis, detachment of the latter at the dermal-epidermal junction, inflammatory hyperaemia involving the small vessels in the corium and slight perivascular exudation of neutrophils and round cells. Less severely affected parts of the epidermis presented more subtle changes consisting of intra-epidermal cleavage between the stratum corneum and the malpighian layer, which occasionally extended into the pilo-sebaceous follicles, vacuolation of cells in the malpighian layer and variability in nuclear staining throughout the epidermis.

Lungs.—Sections showed nodular bronchopneumonic consolidation with abscess formation and cavitation on a small scale. Exuberant mycelia with hyphae and fruiting heads were found in the pneumonic foci. The fungus was identified as *Aspergillus fumigatus*. No granulomatous lesions were found and there was no sign of dissemination to other organs.

Other organs and tissues.—No relevant abnormalities were detected.

Discussion.

Clinically and pathologically this was a typical example of toxic epidermal necrolysis. The aetiology of the condition in this case, however, is by no means certain. Anti-tetanic serum, pethidine, atropine, paraldehyde and a blood transfusion were given within eleven days of the onset of the rash. There was also a history of trauma and pulmonary aspergillosis was found at autopsy. This was a true aspergillus bronchopneumonia in that the fungus was present in the pulmonary tissue and was not just a contaminant in the sputum. The absence of granulomatous lesions suggested that the pneumonia was of recent origin. Although the relationship of the pneumonia to the skin changes is doubtful, skin rashes are known to be occasionally associated with disseminated aspergillosis (Grcevic and Matthews, 1959).

Toxic epidermal necrolysis is a characteristic clinical and pathological entity. At least twenty-seven cases, including the present, have been reported, and

seven of these patients have died. The condition occurs at all ages and two females have been affected for every male. The present patient, who was 85 years old, is the oldest reported, the youngest being a Zulu baby of five months (Walker, 1959).

Recurrent attacks have occurred in six cases, and one of Lyell's patients had five attacks. Sometimes previous attacks have been diagnosed as pemphigus (Rook, 1957 ; Gill, 1958). Patients may give a previous history of other toxic eruptions. One of the cases of Lang and Walker (1957) had had erythema multiforme due to phenolphthalein and another, the Stevens-Johnson syndrome due to the same drug. A third case was known to be sensitive to penicillin ointment. Ruskin's (1948) epileptic girl had had rashes with diphenylhydantoin sodium, phenobarbitone and sulphonamides. Hypermelanotic fixed eruptions due to phenophthalein and dapsone, respectively, preceded episodes of toxic epidermal necrolysis in two cases described by Browne and Ridge (1961).

The condition may represent a toxic reaction to a variety of factors. Drugs possibly incriminated include methylphenylethyl hydantoin (Ruskin, 1948), gold salts (Jaeger, 1951) oil of chenopodium (Lang and Walker, 1956), phenylbutazone (Lyell, 1956), phenolphthalein (Lang and Walker, 1957 ; Browne and Ridge, 1961), penicillin (Lang and Walker, 1957), antipyrin (Kennedy *et al.*, 1957), acetazolamide (Ellis, 1957), tetrachlorethylene or amytal (Gill, 1958), saridone (Soltermann, 1959), tetracycline and promezathine (Evans, 1959), penicillin and sulphonamides (Potter *et al.*, 1960) and dapsone (Browne and Ridge, 1961). In the present case anti-tetanic serum, atropine, pethidine and paraldehyde had all been given within eleven days of the onset of the rash. In reported cases the time interval between administration of the drug and onset of the condition ranges from a few hours to twenty-one days.

In other cases the eruption has been preceded by pain in the loin (Lyell, 1956), sore throat (Lyell, 1956), diarrhoea (Rook 1957), vomiting and impetigo (Catto, 1959) or upper respiratory infection and otitis media (Potter *et al.*, 1960). Lyell's third case was found at autopsy to have acute glomerulonephritis with abscesses in the brain and spleen. Occasionally no precipitating factor at all can be found (Lang and Walker, 1957).

The eruption usually follows a constant pattern. The first change is a blotchy erythema, often on the buttocks and thighs. The skin may be tender and within a few hours the skin loosens and flaccid bullae appear. Complete separation may occur, especially in areas exposed to friction, leaving tender, red, raw oozing areas. Apparently normal skin may be loosened by the finger, as in the Nikolsky test. Bullae may be absent, as in Lyell's third case, and it has been suggested that this may have been the result of dehydration. Between 20 and 80% of the skin surface may be shed. Occasionally haemorrhagic purplish macules are a feature (Lang and Walker, 1957). Involvement of the penis, scrotum, vagina and perianal region has been reported and sometimes a purulent

balanitis may be found. The mouth is affected in more than half the cases. Bullae, haemorrhagic ulcerative stomatitis with crusting of the lips or membranous tonsillitis may occur. Involvement of the eyes occurs in more than one third of the cases. Puffiness of the eyes can be followed by a purulent conjunctivitis and matting of the lids. Haemorrhagic crusts may form on the lids and shedding of the lashes has occurred. In the majority of cases the temperature is raised up to 106° F., but occasionally it may be normal, even when the patient is desperately ill. In a few cases the temperature may rise later, presumably due to toxic absorption. The eruption rapidly reaches a peak and thereafter no fresh shedding occurs. Healing takes place without scarring, usually in two or three weeks, although there may be slight disturbance of pigmentation in the affected areas. The nails and most of the hair were later shed in Lyell's fourth case.

Investigations, even at the height of the illness, have revealed surprisingly little information. The white cell count is usually normal, in the absence of infection. There may be slight albuminuria. Several patients have been investigated for abnormal porphyrin metabolism with negative results. The serum proteins are usually normal. In one patient reported by Frain-Bell and Koblenzer (1959), virological studies of the blister fluid were negative.

The primary pathological change in the skin is epidermal necrosis varying from localized patchy loss of the malpighian layer (Rook, 1957) to widespread disruption of all the layers of the epidermis. The plane of cleavage may be intra-epidermal (Lyell, 1956, Case 4; Rook, 1957; Catto, 1959; Soltermann, 1959; Potter *et al.*, 1960) or the whole of the epidermis may separate from the dermis (Lang and Walker, 1956; Lyell, 1956, Case 3). In the present case the plane of cleavage varied in different areas of the body. In Lyell's third case there were marked changes in the hair follicles and sebaceous glands, whereas the sweat glands were normal, suggesting that the hypothetical toxic substance might have been excreted in the sebum. In our case, only occasional pilosebaceous follicles were involved. There is little specific change in the corium.

The patient's comfort and outlook depend largely on good nursing. A turning frame, or air bed, is useful. Oral hygiene is important and infection of the eyes requires treatment with local antibiotic preparations. Dehydration should be corrected, secondary infection prevented by the administration of a suitable antibiotic and pain relieved by analgesics. Steroids have been tried in several cases but their use is debatable.

We regard this condition as a toxic eruption which may result from a variety of causes including drugs, infections, either bacterial, viral or fungal, blood diseases, reticuloses or metabolic disorders. Epidermolysis necroticans combustiformis was suggested as an alternative name by Soltermann (1959) and the condition was likened to acute pemphigus by others (Potter *et al.*, 1960). We prefer to retain Lyell's original term, toxic epidermal necrolysis.

Summary.

A patient with toxic epidermal necrolysis is described. Bronchopneumonia due to *Aspergillus fumigatus* was found at autopsy.

We wish to thank Mr. J. M. P. Clark under whose care the patient was admitted, and Dr. C. J. La Touche for confirming the diagnosis of aspergillosis.

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Addendum.

Since this paper was submitted for publication, two further cases have been seen by one of us (N. R. R.) One was due to phenylbutazone, and the other, in a pregnant woman at term, to phenobarbitone. Both showed yellowish-brown areas of "tanning" similar to those described in the case above, in addition to red raw areas and flaccid bullae. Histological examination of the tanned areas in the first of these cases showed necrosis and other changes in the dermis, as well as typical appearances in the epidermis. The histology of these cases will be reported in detail later.

PLANT DERMATITIS.

The Significance of Variety-Specific Sensitization.

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It is now well recognized that allergic sensitivity to a plant may be restricted to a single botanical species, or may extend to related species in the same genus and to other genera in the same family (Rook, 1960, 1961). It appears to be less widely appreciated that sensitivity may be confined to one or a few horticultural varieties of certain common garden plants, although there are several incidental references to this phenomenon in the literature. The object of this present article is to report three new cases and to discuss the theoretical interest and practical significance of what appears to be a common occurrence.

To the botanist a variety is a population within a species, this population bearing several distinctive and inheritable characters. The horticulturalist applies the term less rigidly to " any plant with distinctive characters not worthy of specific rank, the characters being permanent in that they can be maintained by vegetative or seminal propagation " (Stearn, 1951). A horticultural variety (sometimes called a cultivar) is a variety or race subordinate to a species that has originated and persisted under cultivation. Horticultural varieties may be produced in several different ways. (Crane and Lawrence, 1952). They may be the result of careful selection and breeding within a single species, as in the case of *Primula obconica* (Hill, 1912) and will then come more or less true from seed. The horticulturalist has merely taken advantage of inherent genetic changes. Many other garden plants have been produced from two or more wild species by generations of hybridizing, as in the chrysanthemum and pelargonium (" geranium ") and many of the tulips. Such hybrids must be propagated vegetatively and every individual specimen is then part of the same clone and all are necessarily identical in all respects. Still other varieties have resulted from spontaneous autopolyploidy : some of the best known tulips and hyacinths are sterile triploids. Here again propagation must obviously be vegetative.

Case Reports.

Case 1.—A woman aged 57 was the owner of a small general store and greengrocery. For many years she had occasionally sold flowers although this was a very small part of her business. She regularly sold red and yellow tulips in bowls at Christmas and during the next three months sometimes sold as cut flowers tulips of many varieties brought in by local amateur growers. When she attended hospital in January 1951 with a basal-cell epithelioma, she was questioned about mild eczematous dermatitis

of the backs of the hands. This she attributed confidently to her " Christmas tulips ". She was equally confident that she could handle other tulips with impunity. The " Christmas tulips " proved to be of the variety Keizerskroon. A patch test carried out with a leaf three weeks later was strongly positive. Tests with some other unidentified varieties of tulips were negative.

Case 2.—A woman aged 55 had worked as a florist's assistant for 30 years. From December 1954 until March 1955 she suffered from an intensely irritable vesicular dermatitis of the lateral aspect of the left ring finger, the medial aspect of the left middle finger and the lateral aspect of the right ring finger. The tips of both thumbs were thickened and fissured. After March she had no further trouble until December 1955 when the dermatitis recurred in the same distribution and was still present when she was referred to hospital in February 1956. She stated that tulips were responsible for the dermatitis and considered that the variety Rose Copeland was the main offender. Hyacinths and daffodils caused her no trouble, but the lily *Alstroemeria* provoked some skin irritation. Other employees and the proprietor experienced some discomfort from Rose Copeland. Patch tests were carried out with the leaves and stems of the four varieties of tulip which the patient handled most frequently. The reactions after 48 hours were as follows :

Athleet . .	Erythema } primary irritant reaction.
Alberio . .	Erythema }
John Gay . .	Erythema, oedema, papules.
Rose Copeland .	Erythema, oedema, papulovesicles extending beyond area of patch.

Case 3.—A man aged 43 was a gardener employed for 2 years by a chrysanthemum grower. His previous employment as a gardener had involved only casual contact with these plants. He gave no family history of atopic disorders but 2 years ago had been treated for mild asthma which had not recurred. Early in September 1960 he developed an irritable eruption on both forearms which persisted in varying severity. Four or five weeks later his skin and eyelids became red and irritable and the latter became swollen. Throughout this period he was working continuously with chrysanthemums. He was referred to hospital on 27 October and was found to have diffuse oedema, erythema and scaling of the face and the flexor aspects of the forearms. He blamed the chrysanthemums for his trouble and believed that four varieties were mainly responsible. Two weeks later when the dermatitis had cleared, patch tests were carried out with leaves of the sixteen varieties of chrysanthemums grown at the nursery. The tests were read after 48 hours. The leaves of Susan Alesworth, Perfection, James Ryder, Serenus and White Hope, had provoked erythema, oedema and papulovesicles. There was no reaction to the twelve other varieties which included three of the patient's own suspects.

Through the good offices of Mr. John Gilmour, Messrs. H. Shoesmith Ltd. of Woking were approached for information concerning the origin of the varieties concerned. They reported that all the varieties to which the patient reacted were seedlings from an old variety called Snowdonia, which in turn was a seedling from Blanche du Poitou. The varieties to which the patient failed to react were seedlings from many different varieties and were not derived from Snowdonia and had no common parent.

Mechanisms and Incidence.

The chemistry of the substances producing sensitization or primary irritant dermatitis has been fully elucidated only in the case of the poison-ivy family

and a few plants of economic importance, such as celery and the lemon. There is, however, convincing circumstantial evidence that the sensitizers and irritants all belong to the heterogenous group of non-essential compounds in plants known as secondary products. A genetic factor determines which of the secondary products can be produced by an individual plant although vigour of growth and cultural conditions may influence the relative amounts of these substances present at any given moment. Clearly the capacity of a plant to produce dermatitis is dependent upon the presence of the noxious substance, the quantity in which it is present, and its situation within the plant i.e. the readiness with which the skin can be contaminated.

Plant breeding is designed to increase the horticulturally desirable properties of a plant, such as the colour and form of the flower and the length of the flowering season. These morphological and physiological features are of course genetically determined. It is to be expected that such changes in the genetic constitution of a plant will also modify the range of secondary products and hence involve the possibility of increasing or decreasing the capacity to produce dermatitis. *Primula obconica*, by far the commonest cause of plant dermatitis in Britain, occurs in many varieties, obtained by breeding and selection within the species. All varieties at present commercially available appear to be equally liable to produce dermatitis. Attempts have been made, by hybridizing, with related innocuous species, to breed a harmless variety. Georg Arends, a well-known German horticulturalist, devoted many years to this project, and although he was eventually able to breed a primin-free primula, he demonstrated that reduction of primin content involved reduction in beauty of flower (Teuscher, 1958).

It is instructive to consider in some detail some common plants in which varietal differences in the capacity to produce dermatitis have been recorded or are likely to exist.

Tulips.—The garden tulips, introduced into Europe in the sixteenth century are derived from an unknown hybrid complex (Hall, 1929). The ancestral species, natives of the Near and Middle East, have not been certainly identified. The numerous different forms and varieties have been obtained by selection and crossing of existing hybrids. Dermatitis among bulb handlers and florists is an important and common hazard for the tulip grower. On existing evidence it seems certain that both primary irritant and sensitization dermatitis occurs. Cases 1 and 2 illustrate differences in the sensitizing capacity of tulip varieties. The bulb handlers have long been aware of these differences and for over twenty-five years the variety Rose Copeland has been regarded as the worst offender (Burtwistle, 1935). This variety also enjoys a bad reputation among florists. Van der Werf (1959) found that Preludium most commonly affected those cutting tulips, but he reported one patient who gave much stronger reactions to two other varieties.

Hyacinths.—The florist's hyacinth has been derived by selective breeding from *Hyacinthus orientalis* and its botanical variety, *H. o. provincialis*. Some of the best known varieties such as General de Wet, King of the Blues and Lord Derby, are sterile triploids (Crane and Lawrence, 1952). Primary irritant dermatitis is very common in the bulb fields. Marked differences in the capacity of varieties to produce primary irritation and the much less common but more severe sensitization dermatitis have been noted. Van der Werf (1959) found that L'Innocence, Carnegie and City of Haarlem were the worst offenders.

Narcissi.—The garden narcissi, which of course include the daffodils, are hybrids derived from various combinations of twelve or more wild species of the genus *Narcissus*. Dermatitis, often of great severity, is a serious problem in those cutting and packing the blooms. Either sensitization or primary irritant dermatitis may be provoked. That certain varieties are particularly liable to produce dermatitis has been known at least since 1910 (Walsh, 1910). Van der Werf (1959) has observed varietal differences in the bulb fields of Holland. Information collected during a recent visit to the Isles of Scilly suggested that the varieties Actaea and Princeps were most often incriminated (Bell, 1960).

Chrysanthemums.—The garden chrysanthemums, known collectively as *C. morifolium*, have been evolved through 2500 years by selection and hybridization from wild species of the Far East, of which *C. indicum* and *C. sinense* are the most important. Chrysanthemums are a much more common cause of sensitization dermatitis among both commercial growers and amateurs than is suggested by the paucity of published case reports. Although many growers are inclined to attribute special virulence to certain varieties, this phenomenon was not recorded by dermatologists until Olivier and Renkin (1954) described the case of a horticulturalist with dermatitis of the face and hands who gave a strongly positive patch test to the variety Petite Amie, but no reaction whatever to the eight other varieties which he grew. My Case 3 reacted only to the seedlings of a single parent variety.

Celery.—Celery is *Apium graveolens* and the numerous varieties in cultivation have been obtained by selective breeding within the species. The variety of celery known as Pascal Green grown in the United States was shown to have a greater tendency to produce dermatitis than some other varieties (Wiswell *et al.*, 1948 ; Palumbo and Lynn, 1953).

Pelargonium.—The pelargoniums (garden " geraniums ") have been produced by selective hybridization of a number of wild species of South African origin. The part played by the various species in the formation of the different modern classes has been well reviewed by Clifford (1958). The zonal and the scented pelargoniums are known to cause dermatitis. Varietal differences in sensitizing capacity have not been recorded but seem likely to be present and should be sought.

The Significance of Varietal Differences in Sensitizing Capacity.

Diagnosis.—Patients should always be patch tested with the actual horticultural variety or varieties with which they have been in contact. Unexpected and misleading negative tests may result from the choice of the wrong variety.

Management.—Since desensitization is seldom practicable, the recognition that the patient reacts to only one or a limited number of the varieties he wishes to grow may be of great importance to the commercial grower. By eliminating those varieties to which he reacts he may continue his occupation.

Investigation.—The demonstration by Arends of a genetic linkage between a biochemical character (presence of primin) and a morphological character (size and form of flower) has been mentioned. Careful comparison of the morphological features of the most powerfully sensitizing varieties of other plants, with those that do not sensitize, may make it possible to recognize potential sensitizers by some external character. Of the five varieties to which Case 3 gave positive reactions, four are white or near white and one is pink. None of the varieties to which he failed to react is white. No conclusions can be drawn until many further observations have been recorded.

In the case of plants whose original parent species are known it would be of considerable interest to patch test patients who react to one or more of the modern varieties with any of the parent species which can be obtained.

Summary.

Three cases of plant dermatitis are reported, in which the patients were shown to react to only one or a limited number of the horticultural varieties they handled.

The mechanisms underlying this phenomenon are described and a short account is given of some of the plants concerned. Others likely to manifest this phenomenon are mentioned.

The significance of variety-specific dermatitis is discussed and its practical importance for the patient and the dermatologist is emphasized.

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THE NAILS IN LICHEN PLANUS.

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Lichen planus has long been known to affect the nails and even at times to destroy them but nail changes are generally considered to be rather uncommon and nonspecific (Juliusberg, 1931; Corsi, 1937; Lewis and Ricchiuti, 1940). During observation of 200 patients through the course of their disease, nail changes were noted in 20, or 10%. In none of these cases was there any doubt about the diagnosis of lichen planus and the nail changes developed whilst the disease was active (Samman, in press). This report is based on these twenty cases and fifteen other patients who were either referred to me on account of nail dystrophies or who were known to have lichen planus and were shown to me by colleagues because the nail changes were a prominent feature of their disease. The nail deformities may be considered in three categories.

(i) The change most often seen is a slight longitudinal ridging and roughening of the surface of the nail. It first becomes apparent close to the cuticle and moves forward with the growth of the nail (Fig. 1). This is a very delicate change

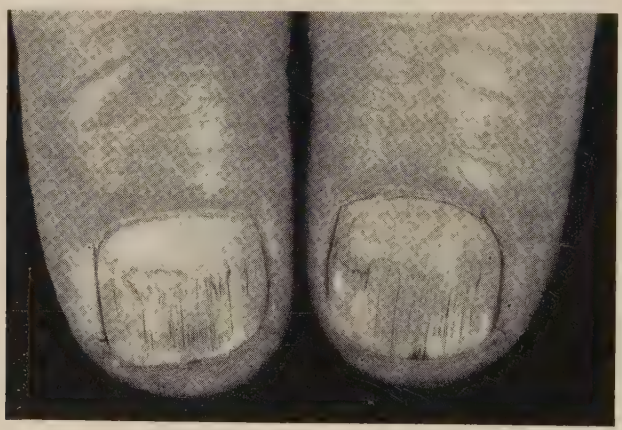

Fig. 1.—The nail plate of two thumb nails returning to normal.

but rather characteristic; it may affect one or all of the nails but not necessarily all at the same time. It is most often seen in cases of widespread lichen planus and there may or may not be signs of inflammation at the base of the nail. It usually becomes visible three to four weeks after the disease becomes widespread. It is often transient. This change can easily be overlooked if the nails are not examined routinely at each visit.

If the process is more severe (Fig. 2), the nail plate will be thinned with more distortion of the nail and restoration to normal is less likely. The ridging is more pronounced, the nail becoming liable to split longitudinally along the ridges. Small pieces may flake off from the surface of the nail. Occasionally in these cases the cuticle grows forward as a pannus and attaches itself to the nail plate. The thin nail is also likely to feel soft and may become spoon-shaped. Permanent damage when it occurs may be restricted to small areas of one or more nails but sometimes the whole nail plate is involved.

Fig. 2.—Damage is more severe. The nail plate is thinned and spoon-shaped and the cuticle has grown forward as a pannus and become attached to the nail plate.

(ii) Worse destruction of the nail is shown by a much coarser roughening starting under the proximal nail fold and moving forward with growth of the nail. This leads to brown discoloration of the nail plate and loss of lustre. Several nails may be involved but again not necessarily all at the same time. This change is very similar to that in some cases of psoriasis of the nails but can be shown to be histologically distinct. Irregular pitting of the surface as in psoriasis is also occasionally seen.

(iii) The most serious change is that which leads to shedding of the nail plate from one or more digits. The loss may be permanent or there may be some regrowth of the nail (Fig. 3). The great toe nails are most often involved. There is usually considerable swelling and bluish discoloration of the skin of the proximal nail fold preceding the shedding of the nail, although typical lichen planus papules are unlikely to be seen in this location. When there is permanent total nail loss in these cases, scarring obliterates any evidence of the nail fold invagination.

All these changes have been recorded by Juliusberg although his report was based mainly on individual case records drawn from the literature. These

indicated that ridging was the most frequent and characteristic change. In addition he referred to cases where there had been great thickening of the nail plate and the nail bed.

There is a rare variety of lichen planus which is almost confined to the feet and is very persistent, lasting many years, leading to painful ulcerations and in the course of time to permanent loss of many toe nails. The diagnosis of these cases may present difficulty but can be established by biopsy. The case reported by Gardner *et al.* (1955) showed features of this type.

Table I records the changes seen in the 20 cases of my series of 200 who showed nail deformities. The total number of changes is greater than 20 as more than

(*a*) (*b*) (*c*)

FIG. 3.—Severe damage. (*a*) The nail plate of the left great toe is becoming loose and there is erythema at the base of the nail. (*b*) The nail has been shed entirely. (*c*) One year later, partial regrowth of a much deformed nail.

one type may be seen in any patient. Some permanent damage was seen in 8 patients, or 4%.

TABLE I.—*Summary of Nail Changes in Twenty Cases.*

	Ridging.	Pitting.	Thinning.	Discoloration.	Shedding.
Temporary	9	2	0	1	0
Permanent	5	0	3	1	3
Total	14	2	3	2	3

The fifteen cases referred to in the first paragraph presented mainly the more severe changes and included the two cases described below where no lichen planus papules could be found on the skin.

The value of recognizing the changes which may occur in lichen planus becomes apparent when determining the cause of acquired nail dystrophies. In the majority of these cases fungus infections, psoriasis or dermatitis can be incriminated but in a few, especially where loss of the nail plate has occurred, lichen planus can be shown to be the cause even in the complete absence of clinical lichen planus elsewhere on the body.

Case Reports.

Case 1.—A man aged 28 was referred on account of nail dystrophies. The right ring finger nail became loose and was shed eight months previously. The left thumb nail underwent a similar change a month later and soon afterwards the left index and left ring finger nails were lost. The right little finger nail started to fall six weeks before the patient was first seen and has since been lost. Three finger nails remain perfect and the toe nails show no abnormality. There has been some attempt at regrowth of some of the lost nails but the plates are thin and brittle and only project 1 to 2 mm. beyond the cuticle. There was no history of previous skin trouble and no evidence of lichen planus elsewhere on the body. A tentative diagnosis of lichen planus was made and nail biopsy arranged. W. R. was negative.

Histology.—One third of the left ring finger nail was removed longitudinally through the matrix and as deeply as possible. The section came away in two layers the upper consisting of the posterior nail fold, the nail plate, the epidermis of the nail matrix and the nail bed. The lower layer consisted of a broad band of lymphocytes situated immediately below the epidermis of the nail matrix and overlying the dermis. The division into two layers could be seen to be due to separation of the epidermis and dermis by this infiltrate.

The patient was subsequently treated with triamcinolone 12 mg. daily for three weeks and the dose was then gradually reduced. This treatment was given in the hope of suppressing the activity of the disease but did not result in any improvement.

Case 2.—A man aged 38 was referred on account of nail dystrophies. The condition had begun three months previously as a roughening of some finger nails starting near the cuticle and gradually extending over the nail plate. This had resulted in ridging and discoloration of the affected nails. The toe nails were normal. Examination revealed grossly distorted nails which superficially resembled those of severe psoriasis. No fungus was found on mycological examination. There was no evidence of psoriasis or lichen planus on the skin but streaking of the oral mucosa was thought to be due to the latter disease. The outer one third of the right ring finger nail with the proximal nail fold, nail matrix and bed attached was removed for histological examination.

Histology.—As in Case 1, the lower part of the biopsy separated during removal. There were two bands of lymphocytic infiltration. The first was a thin band immediately adjacent to the epidermis of the roof of the nail fold invagination and the second a thicker and more vascular band below the epidermis of the nail matrix. There was considerable oedema in this area. The nail plate appeared normal histologically.

Discussion.

The nail plate arises from an invagination of epidermis situated on the dorsum of the distal phalanx of the digits. The proximal third of the roof of this invagination and the floor extending forward as far as the distal edge of the lunule are principally concerned in the formation of the nail plate. Damage to the nail plate may be expected to result from injury of either of these areas. Injury area of the former is reflected in changes seen on the surface of the nail, whilst that of the latter area produces more profound changes.

In lichen planus affecting the nails, biopsy through the whole length of the nail matrix in selected cases has shown a band of lymphocytes in relation to the epidermis forming the roof of the nail fold invagination and a thicker, more vascular and oedematous band in relation to the floor or matrix proper. The

destruction of the nail matrix accompanying this infiltration is probably analagous to the loss of hair matrix following lichen plano-pilaris. The infiltrate does not appear to be confined to small papules but presents as a continuous band. The thin band of infiltrate in the roof of the nail fold is probably associated with minor changes on the nail surface, while the thick band below the matrix proper reflects the more serious damage taking place in this area which may lead to permanent destruction and associated scarring. An infiltrate in the bed below the exposed nail plate is unlikely to be of much importance but may increase the thickness of the nail bed and the nail plate itself when the nail bed is contributing material to the nail plate. Nail biopsies of this type produce permanent disfigurement and can only be justified when the diagnosis is in doubt.

Summary.

The types of nail change seen in lichen planus are described. Some alteration was seen in 10% of 200 cases and permanent damage to one or more nails occurred in 4%. Occasionally, damage may occur in the absence of lichen planus on the skin or in the mouth.

The changes are due to the disease affecting that part of the nail organ which is concerned in the formation of the nail plate.

My thanks are due to my colleagues of St. John's Hospital for referring cases to me and to the Photographic Department of St. John's Hospital for the illustrations. I should also like to thank Mr. Charles Westbury for carrying out the nail biopsies.

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CURRENT LITERATURE

PERSISTENCE OF THE "HYDRALAZINE SYNDROME". E. E. Hildreth, C. E. Biro and T. A. McCreary. (1960) *J. Amer. med. Ass.*, **173**, 657.

Prolonged administration of hydralazine (Apresoline) for reduction of blood pressure produced in about ten per cent of patients a syndrome resembling lupus erythematosus or rheumatoid arthritis. Follow-up of eleven of these patients for periods of three to seven years after stopping hydralazine, revealed continued activity of the syndrome in four cases (raised E.S.R., joint pains, hepatosplenomegaly). G. C. W.

SOAP AND THE MANAGEMENT OF PATIENTS WITH ECZEMATOUS DISEASES. R. B. Stoughton, L. W. Potts, W. Clendenning, S. Fisher and M. Kress. (1960) *J. Amer. med. Ass.*, **173**, 1196.

Two hundred and fifty patients with eczema were given appropriate treatment, but half were forbidden to use soap for hand-washing and bathing, while the rest continued to use it. Patients were unselected and were allotted to the "soap" or "no soap" groups according to a random list. During a five week period progress was assessed by clinicians who did not not know which patients were using soap. The general impression was that the use of soap made no difference to the improvement of the eczema. G. C. W.

WEGENER'S GRANULOMATOSIS—A TRIAD. J. B. McDonald and R. W. Edwards. (1960) *J. Amer. med. Ass.*, **173**, 1205.

A case report of this rare type of granulomatosis is described in a man aged 57. Intractable sinusitis, leading to atrophy and ulceration in the upper respiratory tract, was followed by nodular lung involvement and fatal glomerulonephritis. Widespread necrotizing granulomatous infiltrations together with vasculitis had caused destruction in the lungs, nasal passages, skull, and kidneys. The triad of systemic involvement (nasal passages, lungs and kidneys) with destructive granulomatosis of unknown etiology is characteristic of Wegener's granulomatosis. It is thought to be distinct from polyarteritis nodosa and from midline granuloma of the nose. When the skin is involved, the lesions are said to be haemorrhagic and bullous. G. C. W.

PHOTOBIOLOGICAL RESEARCH WITH PARTICULAR REFERENCE TO SKIN. H. F. Blum. (1960) *J. Amer. med. Ass.*, **173**, 1353.

In a report to the American Committee on Cosmetics, Professor Blum surveys the photobiological responses of the skin in relation to chromophores and their action and absorption spectra. He discusses the use of monochromatic and polychromatic light in research on light sensitivity and carcinogenesis, and he remarks on recent experimental animal work in the field of carcinogenesis using ultraviolet light. G. C. W.

THE AGED HUMAN SEBACEOUS GLAND. J. Graham Smith, Jr. (1959) *Arch. Derm., Chicago*, **80**, 663.

Sebaceous gland excretion was measured by utilizing the reduction of osmic acid by sebum absorbed on filter paper. It was confirmed that there was no significant difference in the sebaceous gland excretion of the adolescent male and female, nor in that of the aged and adolescent male, but there was a decrease in excretion of the glands of the aged female compared with the adolescent.

It was found that the aged male sebaceous gland responded to parenteral testosterone by increased secretion and that the aged female gland responded to a less extent to parenteral progesterone. These increases were temporary. J. K.

NEUTRON ACTIVATION ANALYSIS OF ARSENIC IN NORMAL SKIN, KERATOSES AND EPITHELIOMAS. A. N. Domonkos. (1959) *Arch. Derm., Chicago*, **80**, 672.

In the majority of cases, less arsenic was found in epitheliomas than in the surrounding skin whether the patient had been taking arsenic or not. There was slightly greater amount of arsenic in normal skin of patients who have been taking arsenic. There was no difference in the amount of arsenic in epitheliomas whether patients have been taking arsenic or not. The amount of arsenic in the skin seems to have no significant bearing on the development of cancer. J. K.

RECURRING CUSHING'S SYNDROME WITH TRICHOPHYTON RUBRUM INFECTION. L. W. Nelson and K. V. McNiece. (1959) *Arch. Derm., Chicago*, **80**, 701.

CUSHING'S SYNDROME AND DERMATOMYCOSIS. O. Canizares, H. Shatin and A. J. Kellert. (1959) *Arch. Derm., Chicago*, **80**, 705.

The first article records one and the second three instances of extensive spread of *T. rubrum* infection in cases of Cushing's syndrome. Two patients died but the other two showed marked regression of the tinea infection after adrenalectomy. The authors of the second article explain the dissemination of the infection as a direct result of the effect of excess corticosteroids on the immunological defences of the host. The presence of generalized dermatomycosis with unexplained backache, diabetes or hypertension should make one think of the possibility of Cushing's syndrome.

J. K.

CHONDRODERMATITIS OF THE EARS. L. P. Barker, A. W. Young and W. Sachs. (1960) *Arch. Derm., Chicago*, **81**, 15.

The authors studied 13 patients with nodules of the helix and 7 with nodules of the antihelix. All were in the sixth or later decades. The nodules of the helix were all simple, 12 were in males, all were painful and histology showed a primary cartilaginous lesion with secondary effects in the skin. There was no history of injury. The patients with lesions of the antihelix were six women and one man. The condition was painless and discovered on routine examination. A history of previous trauma was usual. Lesions might be multiple and occur on both ears. Histology showed a primary lesion of the cutis with secondary involvement of cartilage. The two conditions can be regarded as separate clinical entities. J. K.

ACNE, OESTROGENS AND SPERMATOZOA. J. F. Mullins, W. B. McCash and J. K. Lamar. (1960) *Arch. Derm., Chicago*, **81**, 53.

Conjugated oestrogenic substances were given to twenty normal men for three months and a careful check was made of all contents of the sperm count during this period. No significant alteration in spermatogenesis was found. J. K.

PEMPHIGUS, CORTISONE AND PREGNANCY. S. Lapiere. (1960) *Arch. belg. Derm. Syph.*, **16**, 165.

A woman aged 36 after 5 normal pregnancies developed pemphigus. Treatment with 30 to 50 mg. prednisone daily was followed by abortion in the fourth month. A year later she again became pregnant and under treatment with 10 mg. of prednisone daily throughout her pregnancy produced a healthy infant. Only two other recent cases of pemphigus complicated by pregnancy have been found. Both were treated with corticosteroids and both resulted in living children at term, though one died at an early age of a heart defect.

Corticosteroids administered to pregnant women for various reasons have been noted to result sometimes in abortion or congenital defects in full term babies. It has been shown that secretion of corticosteroids rises progressively during the first months of pregnancy till it reaches an average of three times the normal amount by full term. Especially during the first three months of pregnancy corticosteroids should only be given in minimal dosage to give the baby the best chance of survival without congenital malformation. J. K.

SINGLE DOSE THERAPY OF TINEA CAPITIS. L. Friedman, V. J. Derbes and T. A. Tromovitch. (1960) *Arch. Derm., Chicago*, **82**, 415.

A single dose of 3 g. of griseofulvin was given to 22 children with ringworm of the scalp due to *M. audouini*, 21 were cured in from 3–12 weeks and 1 was still infected after 12 weeks but responded to a second dose of 3 g. Of 25 patients similarly affected who were given 1 g. every 1, 2 or 3 days for 28 days all were cured within 12 weeks, 6 patients given 1 g. every 5 days for 28 days were cured, 4 out of 5 patients given 1 g. every 7 days for 28 days were cured, 12 patients given 250 mg. daily for 7–14 days were cured (6 of these had an extra dose of 3 g. as the original dosage was prematurely considered to have failed). A control series of 9 patients given placebo tablets showed 3 cures and 6 failures.

Only 2 patients showed side effects, 1 developed urticaria and 1 nausea. J. K.